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Computational modelling elucidates the mechanism of ciliary regulation in health and disease

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Abstract

Background: Ciliary dysfunction leads to a number of human pathologies, including primary ciliary dyskinesia, nephronophthisis, situs inversus pathology or infertility. The mechanism of cilia beating regulation is complex and despite extensive experimental characterization remains poorly understood. We develop a detailed systems model for calcium, membrane potential and cyclic nucleotide-dependent ciliary motility regulation.Results: The model describes the intimate relationship between calcium and potassium ionic concentrations inside and outside of cilia with membrane voltage and, for the first time, describes a novel type of ciliary excitability which plays the major role in ciliary movement regulation. Our model describes a mechanism that allows ciliary excitation to be robust over a wide physiological range of extracellular ionic concentrations. The model predicts the existence of several dynamic modes of ciliary regulation, such as the generation of intraciliary Ca2+ spike with amplitude proportional to the degree of membrane depolarization, the ability to maintain stable oscillations, monostable multivibrator regimes, all of which are initiated by variability in ionic concentrations that translate into altered membrane voltage.Conclusions: Computational investigation of the model offers several new insights into the underlying molecular mechanisms of ciliary pathologies. According to our analysis, the reported dynamic regulatory modes can be a physiological reaction to alterations in the extracellular environment. However, modification of the dynamic modes, as a result of genetic mutations or environmental conditions, can cause a life threatening pathology.

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